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Specialty Conference

Allergic Rhinitis

Participants: LOUIS M. MENDELSON, M.D., WILLIAM L. NYHAN, M.D., PH.D., AND ROBERT N. HAMBURGER, M.D.

Taken from the weekly Pediatric Grand Rounds held at the University Hospital of San Diego County, University of California, San Diego, School of Medicine, November 9, 1971

DR. MENDELSON:* *Case 1.* The patient was an 8-year-old boy referred to the Allergy Clinic for evaluation of possible nasal allergy. The child was entirely well until about three years of age when, following exposure to freshly cut grass, rhinorrhea, paroxysmal sneezing, and itching of the nose developed. He also complained of watery and itchy eyes. These symptoms then continued and occurred perennially, with somewhat lessened severity in the winter. He was awakened two or three nights a week by sneezing and nasal obstruction. He was always lethargic and irritable, and because of his nasal problems he found it difficult to participate in outdoor activities with other children. He used two handkerchiefs a day. His teacher constantly complained about the noise he made when he breathed and said it disturbed others in class. He was being treated with Actifed®†, which helped control the sneezing but made him sleepy.

The nasal discharge was clear and watery. The patient constantly rubbed his nose (the "allergic salute") and made a clicking noise with his tongue because of an itchy palate. His eyes always had dark circles ("shiners") under them.

As an infant he had eczema, but he had not had this problem for the previous five years. There was no history of asthma and no drug or food intolerance.

His mother had had a life long history of rhinitis and asthma. The father and 17-year-old sibling had no history of allergic disease.

There was a history that grass, house dust, and cats could produce nasal symptoms. Other physical findings in the patient included the presence of facial grimacing, allergic salute, a nasal crease, and allergic shiners. The nasal mucosa was pale and boggy, and there was mild nasal obstruction.

Laboratory data showed numerous eosinophils on nasal smear. There was an elevated serum concentration of gamma E immunoglobulin (IgE). Skin tests for reaction to grass, dust and cat danders were immediately positive.

Case 2. The patient, an 8-year-old boy, was referred to the Allergy Clinic for evaluation of noisy breathing which he had had since birth. He had first sought help for this problem two

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†Generic names of proprietary agents mentioned are listed at the end of this article.

years previously. A diagnosis of allergic rhinitis had been made and Chlortrimeton Syrup® prescribed. Subsequently, he was seen several times for the same problem and each time was treated with Dimetapp® and Actifed®. The use of these medications led to minimal improvement of the noisy breathing. His nasal obstruction and noisy breathing were perennial but worse in the winter. In addition, the breathing became more obstructed when he acquired an upper respiratory infection. He did not sneeze. His nose did not itch, and there was no rhinorrhea. He did not have an allergic salute. His nose became obstructed when subjected to extreme changes in temperature or humidity as when going from outdoors into an air-conditioned environment. He had had only one ear infection in his life and rarely had sore throat. There was no history of eczema, hives, drug sensitivity, or intolerance to foods. He had once been stung by an insect, with no significant reaction. He had no symptoms referable to the eyes, he did not cough or wheeze, his exercise tolerance was excellent and his general health was good.

The mother, father, and two siblings had no allergic disease.

Physical examination revealed no significant amount of tonsillar or posterior pharyngeal lymphoid tissue. No posterior pharyngeal discharge was present. Breathing was not obstructed and the nasal passages were dry. The inferior turbinates, especially on the left, were somewhat enlarged. The color of the mucous membranes was normal.

There were very few eosinophils in a smear of material from the nose. Skin testing for sensitivity to ten common inhalants revealed no significant reactions.

Discussion

Rhinitis is one of the most common problems we deal with in the practice of medicine. This is especially true in pediatrics. One of the most common causes of rhinitis is allergy. According to the latest figures from the National Center for Health Statistics, 31 million Americans have one or more allergic disorders, and of these, approximately 13 million have pure allergic rhinitis.[1] Table 1 lists the prevalence of chronic diseases in children. Allergic disorders lead the list.[2] Approximately $135 million is spent annually on prescription drugs for allergic conditions. There is no telling how much is spent for over-the-counter medication.

TABLE 1.—*Prevalence of Selected Chronic Conditions per 1,000 Children under Age 17, by Sex; United States, July 1966-June 1967*

Condition	*Boys*	*Girls*
Hayfever, asthma and other allergies	106.7	90.2
Respiratory conditions	59.9	51.0
Orthopedic impairments and paralysis	24.8	22.0
Speech, hearing and visual impairments	28.1	16.9
Skin infections and diseases	14.3	15.8
Digestive system conditions	13.2	8.5
Mental and nervous conditions	7.3	6.0

Clinical immunologic reactions can be divided into four categories, using the Gell and Coombs classification.[3] Allergic reactions are classified as Type I reactions. These reactions are characterized by the combination of antigen with an antibody. The antibody is fixed to a target cell, which, in the case of allergic rhinitis, is the mast cell. The interaction of the antigen with the antibody causes the release of a mediator, such as histamine, from the target cell. The mediator in turn acts on the target tissue, which in the case of rhinitis is the group of small blood vessels in the nasal mucosa. In this way the symptoms are produced.

The major source of antibody involved in the allergic reaction is IgE.[4] One of the properties that distinguishes IgE from other antibodies is its ability to fix either to mast cells or to basophils, both of which are rich in histamine.

The exact mechanism of the release of histamine is not known. Work by Stanworth suggests that when the antigen combines with IgE, it causes an activating site on the IgE to be exposed, thus facilitating the attachment of this site to a similar site on the mast cell (Figure 1). This reaction then precipitates the release of histamine.[5]

Much has been learned about the mechanism of the release of histamine by the use of the human leucocyte histamine release technique.[6] In essence, this procedure takes advantage of the fact that basophils which contain histamine also fix IgE. The test is performed by mixing basophils which have IgE fixed to them with an antigen and measuring the amount of histamine released. Using this technique the following

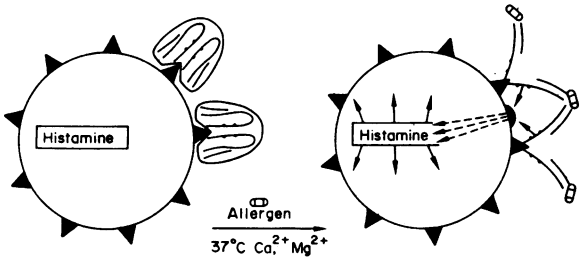

Figure 1.—Postulated manner in which the interaction between cell-bound γ E antibody and allergen triggers the release of vasoactive amines. (Reprinted with permission from Clinical Allergy (1:27, 1971).)

things have been learned: (1) IgE sensitizes basophils. (2) Histamine is preformed in the basophil. (3) The basophil is not destroyed by the histamine release. (4) Complement is not needed for the reaction to take place. (5) Cyclic 3,5-AMP is important in the regulation of the release of histamine.

This neat picture of the Type I reaction does not explain all of the phenomena that we see in clinical allergic rhinitis. For example, a person may inhale large amounts of ragweed pollen in the laboratory out of ragweed season and have no symptoms; yet if he inhales even a small amount during the ragweed season he gets severe symptoms.

To explore this question, John Connell at the Roosevelt Hospital in New York performed what are now considered classic experiments leading to an understanding of allergic rhinitis.[7] With the aid of two instruments which he developed, he was able to produce acute episodes of allergic rhinitis in an individual nostril with a measured number of pollen grains. Concomitantly he measured nasal patency. The latter was an objective measurement of clinical response.

With successive daily nasal challenges out of ragweed season in allergic persons, symptoms began to develop after the second day. By the fifteenth day, one-fortieth the number of pollen grains that caused no symptoms on the first day caused severe nasal obstruction. Connell referred to this as the "priming effect." On day one, 250 pollen grains produced no symptoms; after 15 days of priming 7 pollen grains produced significant obstruction.[8]

Connell next showed that the priming effect was reversible. The time required for reversal depended on the number of days the nostril was primed. After five days of priming, it took three days for the nostril to return to normal, and after five weeks it took four weeks. Similar challenges in non-allergic persons with 5000 times the total dose used in allergic patients produced no obstruction. The priming effect was localized to the nostril primed. As much as 50 times the number of pollen grains that caused severe obstruction on the primed side caused no obstruction on the unprimed side.

Connell's work has also provided an explanation for why people with ragweed-induced allergic rhinitis frequently complain that the only time they have other allergic reactions, for example to cats, is during the ragweed season. He showed that once the nose is primed it will react to any antigen against which the patient has IgE antibodies. At the same time, this was not simply an irritant effect but rather an immunological reaction.[7] A challenge with inert carbon particles of the same size as the pollen grains produced no obstruction.

Nasal biopsy of patients after priming showed fragmentation of the basement membrane. Again, the degree of fragmentation depended on the number of days primed. It is not the number of pollen grains inhaled that causes symptoms but rather the number of antigens that come in contact with IgE. Furthermore, one of the functions of the basement membrane is to keep out foreign antigens. Thus with increased fragmentation of the membrane a greater amount of antigen passes through it and combines with the IgE. Therefore fewer pollen grains need to be inhaled to cause clinical disease.[7]

Clinical Diagnosis of the Disease.

Table 2 lists the three most common causes of rhinitis and the characteristic findings in the history of each. Vasomotor rhinitis refers to chronic rhinitis for which no cause can be found.

Of the cases presented, Case 1 illustrated a classic example of allergic rhinitis. Findings that should make one consider allergy as the cause of rhinitis are the presence of itching in the nose, palate, ears, or eyes (histamine causes itching); paroxysmal sneezing; conjunctivitis; a history of eczema or asthma; a history of attacks of allergic rhinitis precipitated by allergens such as grass, pollen, animal dander, or house dust; seasonal recurrences; or a family history of allergy.

On the other hand, Case 2 was a classic example of vasomotor rhinitis. The patient had

TABLE 2.—*Differential Diagnosis of Rhinitis Historical Aspects*

	Allergic	*Infectious*	*Non-allergic (vasomotor)*
Seasonal incidence	Present seasonally	Absent or worse in winter	Absent or worse in changing season
Recurrences	Mild symptoms present between attacks	Clears completely	Frequently continuous
Family history of allergy	Common	Occasional (coincidental)	Occasional (coincidental)
Constitutional symptoms (sore throat, fever)	Rare	Common	Rare
Other allergic symptoms (asthma, eczema)	Common	Occasional (coincidental)	Occasional (coincidental)
Itching of nose, eyes, palate	Usual	Rare	Unusual
Paroxysmal sneezing	Usual	Rare	Unusual
Allergic salute and nose twitching	Common	Occasional (coincidental)	Occasional (coincidental)
Allergens traced as precipitating factors	Frequent	Unusual	Unusual

This chart is a modification of one in G.M. Sheldon's et al,[17] *a Manual of Clinical Allergy*, W. B. Saunders Co., 1967, Philadelphia.

perennial rhinitis. His nose was very sensitive to changes in weather and temperature. He had none of the allergic symptoms observed in the first patient.

Frequently, the difference between allergic and vasomotor rhinitis is not so clear-cut. The presence of eosinophils in the nasal secretions and elevation of the serum IgE[8] can be helpful in the diagnosis of allergic disease.

Skin testing for immediate reactions is one of the most misused diagnostic tests in medicine. A positive immediate skin test indicates that the patient has skin-fixed antibodies, most likely IgE, to the allergen being tested. It does not necessarily mean that the antigen to which the skin reacts is the cause of the patient's rhinitis. The significance of a positive skin test can only be interpreted in the light of the history. In a patient suspected of having vasomotor rhinitis the absence of positive skin tests can be useful.

Children with perennial rhinitis and a history of frequent formula changes, colic, abdominal pains and leg aches may be allergic to cow's milk.[9] A trial elimination of milk from the diet for a couple of weeks may help. Skin testing for foods offers little help in the diagnosis of rhinitis in children. If a food is suspected the only way to confirm it is by trial elimination and subsequent challenge with the suspected food.

In obtaining the history it is well to devote a good deal of time to obtaining an idea of how the illness affects the child in his daily living. We are interested in how it affects his sleep at night, his play activities during the day, and his school work. In this way we can judge the severity of the patient's problem. It also provides us with markers to help decide whether he is improving or not with treatment.

There are causes of rhinitis other than the three previously mentioned, which are the most common. A more extensive list is shown in Table 3. Two of these causes are especially noteworthy. The first is foreign body. This diagnosis should be considered in all children with chronic rhinitis, whether or not the rhinitis is unilateral and purulent. The other is rhinitis medicamentosa, which results from the overuse of nasal drops or sprays. Many patients use topical vasoconstrictors to alleviate their nasal obstruction, and at first they obtain immediate relief. However, after days of continued use rebound occurs and a vicious cycle is established.

Treatment

The treatment of allergic rhinitis can be divided into the three following categories: (1) avoidance of allergens to prevent allergic symptoms; (2) pharmacological treatment to minimize or counteract the consequences of exposure once it has occurred; and (3) immunological treatment to alter the immunologic response to the allergens.

In avoidance therapy we try to get the patient to avoid, as much as possible, all of the allergens

TABLE 3.—*Diagnosis of Rhinitis*

FOREIGN BODY	ALLERGY
ANATOMIC VARIATION	1. Seasonal hayfever or pollinosis
1. Adenoid hypertrophy	2. Perennial allergic rhinitis
2. Choanal occlusion	
3. Deviated septum	
NEOPLASM	INFECTIONS
1. Sarcoma	1. Common cold
2. Polyps	2. Purulent rhinitis
a. Cystic fibrosis	3. Adenoiditis
b. Allergy	4. Sinusitis
c. Aspirin	5. Diphtheria
	6. Kartagener syndrome
INJURY	ENDOCRINOLOGY
1. Direct trauma	1. Hypothyroidism
2. Reaction to inhalation fumes	2. Pregnancy
	3. Menstruation
3. Rhinitis medicamentosa	
4. Vasomotor rhinitis	

which cause his disease. Avoidance is most useful in patients with perennial allergic rhinitis in whom house dust, animal danders, molds or other household inhalants are the irritants. It is imperative to obtain a detailed environmental history. In children the area of concentration is the bedroom, because, as Deamer emphasized,[9] a child spends approximately 12 hours a day there. For a child with rhinitis secondary to house dust, we look for a feather pillow, unencased mattress, carpet, and open heating vents, all of which are sources of irritants which can be eliminated and replaced with equally functional items that will not contribute to allergic reactions. We are now training allergy paramedical persons whose work includes helping parents design hypoallergenic environments.

In considering pharmacological treatment, antihistamines are the principal agents used in the management of allergic rhinitis. They work by competing with histamine for the target cell (or, in rhinitis, the blood vessel), not by inhibiting the release from the mast cell.

Antihistamines fall into five different classes, based on their chemical structure (Table 4).[10] These are ethanolamines, ethylenediamines, alkylamines, piperazines, and phenothiazines. The side effects tend to be similar in all members of any one group. If a patient does not respond well or has side effects from brompheniramine, which is in the alkylamine class, it would be wise not to select chlorpheniramine because it is in the same class. A better choice would be an ethylenediamine such as tripelennamine. We find this chart useful because it is often difficult to remember which antihistamine is in which group.

Antihistamines are useful for rhinorrhea, nasal itch, and paroxysmal sneezing. They are not nearly as effective against nasal obstruction as a vasoconstrictor such as ephedrine, pseudoephedrine, phenylephrine or phenylpropanolamine. Frequently these sympathomimetic drugs are combined with antihistamines. Their stimulatory effect offsets the sedative effect of antihistamines. Table 5 lists some of the most frequently used combinations. We use this table as much as we do Table 4. For example, if Actifed® does not seem to be effective, we do not prescribe Dimetapp®; rather we use Rondec® which has an ethanolamine antihistamine.[10] Frequently, anticholinergic agents, either alone or combined with antihistamines and sympathomimetrics, are helpful in rhinorrhea. Examples of such preparations are Ornade® and Extendryl.®

Systemic steroids are rarely indicated in patients with allergic rhinitis. However, in a very few patients in whom the rhinitis still hampers daily activities, in spite of optimal treatment, a short course of dexamethasone sodium phosphate (Decadron®) nasal spray (marketed as Turbinaire®) often gives excellent results.[11] Turbinaire in recommended dosages has a systemic absorption equivalent to approximately 4 mg of prednisone. This can be adrenosuppressive.[12]

Immunotherapy involves giving a series of subcutaneous injections of antigen in increasing amounts with the goal of injecting the highest concentration the patient can tolerate without severe local or systemic reactions. Immunotherapy is one of the most controversial subjects in allergy. However, a double-blind study reported by Sadan, et al in 1969[13] clearly demonstrated its effectiveness in children with ragweed-induced hay fever and allergic rhinitis. This study involved 35 patients, 18 of whom were treated with immunotherapy. In Chart 1, the relative severity of symptoms is shown on the ordinate. After immunotherapy 13 of the 18 treated patients had lower scores than any of the controls.

Lichtenstein and colleagues[14] have shown that immunotherapy has three immunologic effects in allergic rhinitis. First, it causes an increase in blocking antibodies, usually gamma G and gamma

TABLE 4.—*Antihistamines*

Class	*Drug*	*Side Effect*
Ethanolamines (I)	Diphenhydramine hydrochloride (Benadryl®)	Pronounced sedation
	Carbinoxamine maleate (Clistin®)	
Ethylenediamines (II)	Tripelennamine hydrochloride (Pyribenzamine®)	Moderate sedation, occasional nausea
Alkylamines (III)	Chlorpheniramine maleate (Chlortrimerton®)	Slight sedation
	Brompheniramine (Dimetane®)	
Piperazines (IV)	Cyclizine hydrochloride (Tacaryl®)	Slight sedation
Phenothiazines (V)	Promethazine hydrochloride (Phenergan®)	Pronounced sedation

TABLE 5.—*Antihistamine Combinations in Common Use*

Drug	*Antihistamine*	*Nasal Decongestant*	*Other*
Actifed® Syrup	Triprolidine hydrochloride (I) 25 mg	Pseudoephedrine hydrochloride 30 mg	
Actifed® Tablet	Triprolidine hydrochloride (III) 2.5 mg	Pseudoephedrine hydrochloride 60 mg	
Dimetapp® Elixir	Brompheniramine maleate 4 mg	Phenylephrine hydrochloride 5 mg	
		Phenylpropanolamine hydrochloride 5 mg	
Dimetapp® Extentab	Brompheniramine maleate (III) 12 mg	Phenylephrine hydrochloride 15 mg	
		Phenylpropanolamine hydrochloride 15 mg	
Drixoral®	Dexbrompheniramine maleate (III) 6 mg	D-Isoephedrine 120 mg	
Copyrinol®	Pyrrobutamine (III) 15 mg	Thenylpyramine (II) 25 mg	Cyclopentamine 12.5 mg
Novahistine®	Chlorpheniramine maleate (III) 1.0 mg	Phenylephrine hydrochloride 5.0 mg	
Ornade®	Chlorpheniramine maleate (III) 8 mg	Phenylpropanolamine hydrochloride 50 mg	Isopropamide 2.5 mg
Triaminic®	Pyrilamine (II) 25 mg	Phenylpropanolamine hydrochloride 50 mg	
Rondec®	Carbinoxamine maleate 2.5 mg	Pseudoephedrine hydrochloride 60 mg	

M immunoglobulins (IgG and IgM) that combine with the antigen and prevent it from coming in contact with the IgE antibody.[13] Second, the IgE specific for the antigen decreases.[15] Normally in an untreated allergic person the IgE for the antigen increases during the season and somewhat decreases after the season. During the first year of treatment, IgE levels were noted to increase early in immunotherapy and then slowly to decrease. After the second year of therapy there was no rise when the pollen season started. By the end of the pollen season there may actually

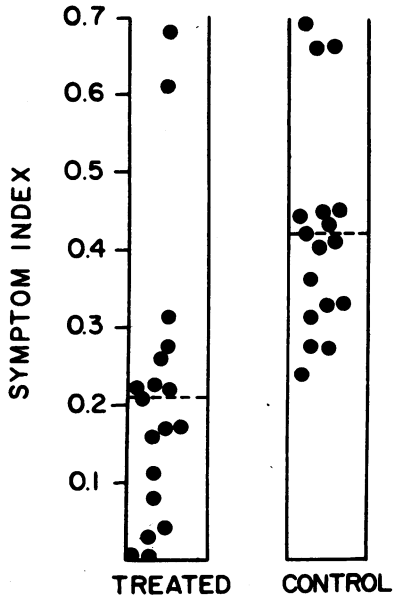

Chart 1.—Symptom indices of the 18 treated and 17 control children of Sadan's study. (Reprinted with permission from N Engl J Med (280:625, 1969).)

be a decrease in the amount of IgE in treated patients. The third effect is that after immunotherapy the ability of the cell to release histamine decreases.[13] In a manner similar to the decreased sensitivity of patients to some drugs with repeated use, immunotherapy lessens or completely stops the patient's reaction to antigen challenge.

In summary, I have reviewed with you what is known about the pathogenesis, diagnosis and treatment of allergic rhinitis, with the hope that this will aid in the treatment of this very common problem.

QUESTION FROM THE AUDIENCE: Would you comment on environmental controls. It is my impression that most of my patients whose symptoms should have improved with alteration of their environment did not seem to have been helped.

DR. MENDELSON: We find that the key is in how we instruct our patients or their parents in environmental control. Instruction sheets are seldom useful without a very specific review of the child's specific environment. In our department, Mrs. Judy Lee Bachman, who is an expert on avoidance procedures in the allergic patient's environment, makes visits to the home. Mrs. Bachman and her trainees take a detailed environmental history and, when indicated, make the home visit. On the visit, the sources of allergens in the patient's room are pointed out. Detailed advice is given on how to rid the rooms of these sources. Also the families are told where they can get any materials they need to produce hypoallergenic rooms. Each family and each referring physician is provided with a detailed report of the allergy physician's assistant's visit. We have been very impressed with the numbers of patients whose symptoms have been improved by environmental controls alone when these procedures are carefully followed.

QUESTION: Would you comment on nasal polyps and allergy?

DR. MENDELSON: Nasal polyps are very uncommon in children with allergic rhinitis. If one finds nasal polyps in a child, cystic fibrosis must be ruled out first. In an adult, one considers aspirin sensitivity. If these causes of polyps have been dismissed in a patient with allergic rhinitis, most experts feel that the polyps are secondary to a superimposed chronic infection. Unless nasal polyps are causing severe symptoms, they should not be removed because of the frequency and rapidity of recurrence.

DR. NYHAN:* In your experience, what proportion of patients do you treat with one or another of the three methods you mentioned.

DR. MENDELSON: Most of my patients are managed by avoidance therapy and pharmacological treatment. However, in a referral practice where you get only the most difficult cases, most require immunotherapy. Perhaps Dr. Hamburger would comment on this.

DR. HAMBURGER:† In a large, predominantly pediatric allergy practice where the allergists are conservative and employ allergy physician's assistants or environmentalists, I would say that approximately one-third of the patients can be managed by environmental controls. An additional third will be improved by the addition of medication. The remaining one-third will require immunotherapy as an adjunct to medications and attention to the environment. Dr. Kemp** tells me that in his experience and that of other pediatric allergists in private practice, approximately the same distribution of response to therapy is observed.

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combination of chlorpheniramine maleate with phenylpropanolamine hydrochloride, and isopropamide iodide

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combination of carbinoxamine maleate and pseudoephedrine hydrochloride

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OUT, LARGE STONE!

What should be done when x-rays reveal a large solitary stone in the gallbladder?

Most surgeons agree that if it is symptomatic, a cholecystectomy should be performed. However, some believe that if the stone is asymptomatic cholecystectomy is not necessary. I believe that a large solitary stone in the gallbladder presents a real hazard. It cannot pass through the cystic duct and often if it becomes lodged in the neck of the gallbladder it produces a rapidly developing and serious group of complications. These may include acute cholecystitis, gangrene of the gallbladder, and perforation with necrosis of its wall. The stone may erode into adjacent structures, including the common bile duct, the duodenum, the stomach, the colon or the pelvis of the kidney; and it has even been reported to have eroded into ovarian cysts and through the abdominal wall.

In a series of 300 consecutive biliary tract operations I found either patent or healed spontaneous internal biliary fistules in 22 patients. This is a high incidence, higher than is usually reported, and higher than in my complete series where the incidence of spontaneous internal biliary fistulae runs approximately 3 percent. With a patent fistula and especially into the colon an ascending cholangitis can be very severe and produce marked hepatic damage. Also if a large stone passes into the small bowel it may produce small bowel obstruction. Therefore I am convinced that when a large solitary stone is found in the gallbladder, irrespective of whether it is asymptomatic or symptomatic, a cholecystectomy should be performed if the patient's condition permits.

—CHARLES B. PUESTOW, M.D., Chicago

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